

SHORT COMMUNICATIONS

Catalytic Properties of Cyclodextrin for Selective C–O Bond Formation

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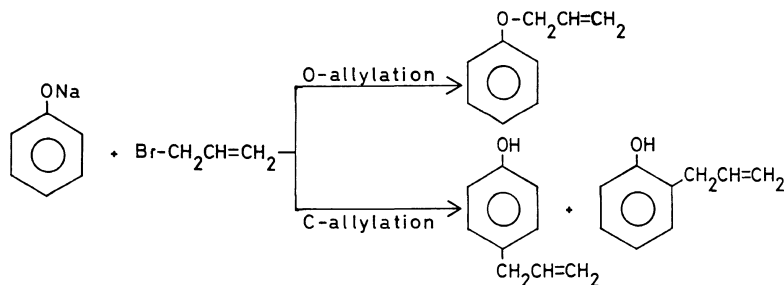
Cyclodextrin (CyD)¹ has been of interest from the viewpoint of enzyme-mimetic chemistry. In an aqueous medium, it is capable of recognizing a substrate molecule,² and accelerating its reaction like an enzyme. In these enzyme-mimetic reactions, however, the hydrophobic cavity of CyD mainly does nothing but act as a binding site to fix the substrate in a certain conformation.^{1,3–5}

Recently it has been found that CyDs can accelerate not only the bond cleavage reaction but also the bond formation reaction.^{6–11} For example, Diels-Alder cycloadditions were accelerated in an aqueous medium in the presence of β -CyD,^{6,7} vitamin K₁ (or K₂) analogues were synthesized from 2-methylhydro-1,4-naphthoquinone and alkyl bromide using β -CyD as a catalyst,⁸ and 4-hydroxybenzaldehyde, 4-hydroxybenzoic acid and 4-hydroxy-

methylphenol were selectively prepared from phenol in the presence of β -CyD.^{9–11} The selective C–O bond formation, however, has never been achieved in water by the catalysis of CyD.

In the case of the Williamson reaction between phenol (or phenolate) and alkyl halide in an organic hydrophobic solvent, the reaction produces alkyl phenyl ether selectively. In an aqueous medium, however, the reaction proceeds slowly and the selectivity of the products (ratio of O-allylation products to C-allylation products) decreases considerably due to solvation by water molecules which prevent the anionic oxygen atom of phenolates from attacking the allylating reagent, resulting in C-allylation.^{12–14} (*cf.* Scheme 1)

Here, we have successfully developed a new system using a CyD cavity as a reaction field



Scheme 1.

for the C–O bond formation. The allylation of phenol is carried out in water in the presence of CyD to produce allyl phenyl ether selectively using only the hydrophobic cavity. In addition, an organic reaction in water is not only instructive from the viewpoint of enzyme-mimetic chemistry but also greatly facilitates practical organic syntheses. For example, water is less toxic than organic solvents and makes it easy to separate products from reaction mixtures.

EXPERIMENTAL

A typical reaction was carried out as follows. In a 50 ml flask, 1.2 mmol of phenol and 1.4 mmol of CyD were mixed in 30 ml of a sodium carbonate buffer solution (pH 11) and the mixtures were stirred for 16 h at 28°C. After incubation, the oily phenol was dissolved. Then 1.0 mmol of allyl bromide (3-bromo-1-propene) was added and the mixtures were incubated for 20 h at 28°C. After the reaction, the mixtures were acidified with a dilute solution of hydrochloric acid. The precipitated catalyst and aqueous solution were washed three times with 100 ml of diethyl ether. The ethereal solution was collected, and dried with anhydrous Na₂SO₄ and anhydrous MgSO₄. The ether was evaporated and the residue was analyzed by HPLC (Column: TSK gel, ODS-80-TM, Tosoh Co. Eluent: methanol–water, v/v ratio = 6 : 4).

RESULTS AND DISCUSSION

The yields and selectivities of the products are listed in Table I. Trace amounts of side products, for example the double alkylation products of phenol, were detected and the unreacted phenol was recovered. β - and γ -CyDs work as effective catalysts for the selective synthesis of allyl phenyl ether (phenyl 2-propenyl ether). The low selectivities for D-glucose and amylose-A indicate that not the glucose moieties but the hydrophobic cavities of

Table I. Alkylation of phenol with allyl bromide in water with and without various additives^a

Additive (amount in mmol)	Yield ^b of allylation %		Selectivity for <i>O</i> -allylation %	
	<i>O</i> -	<i>C</i> -		
None	—	29	26	53
D-Glucose	11.2 ^c	26	18	59
Amylose A ^d	(11.2)	23	23	50
α -CyD	1.4	15	21	42
β -CyD	1.4	55	8	87
γ -CyD	1.4	46	4	92

^a The reaction was carried at 28°C for 20 h using 1.2 mmol of phenol and 1.0 mmol of allyl bromide in 30 ml of pH 11 buffer.

^b The yields are based on the amount of allyl bromide. Unreacted phenol was recovered and by-products were detected in small amounts.

^c The same quantity as that used in the case of γ -CyD in a glucose unit, since γ -CyD is composed of 8 glucose units.

^d The average molecular weight of amylose A used here is approximately 2900. The same quantity as that of D-glucose was used.

CyDs are essential to the selective catalysis. Although all CyD derivatives have hydrophobic cavities, β - and γ -CyDs work as selective catalysts, but α -CyD does not.

As described above, the selectivity of the Williamson reaction depends on the hydrophobic atmosphere of the solvent.^{12–14} In the present experiments, the hydrophobic atmosphere around the anionic oxygen of the phenolate is realized by using β - and γ -CyDs even in an aqueous medium. β - and γ -CyDs have larger hydrophobic cavities than α -CyD so that they may be able to include the phenolate strongly in their cavities in an aqueous medium and desolvate it from water molecules resulting in the selective reaction of C–O bond formation. But the cavity of α -CyD is narrow so that it may not be able to include the phenolate sufficiently, resulting in insufficient desolvation of phenolate from water molecules. This insufficient desolvation or partial solvation of phenolate may hinder the *O*-allylation. In other words, α -CyD cannot offer

an adequate hydrophobic reaction field to promote the O-allylation.

This is supported by the larger association constant of β -CyD with phenol than that of α -CyD.¹⁵ The strong inclusion of phenolate results in increased selectivity of the reaction and in inhibition of the allylation at the benzene ring, because of the steric hindrance by the "wall" of CyD.

In conclusion, we have achieved, for the first time, the selective C–O bond formation in water using CyDs. Since we have been studying the immobilized CyD which creates more hydrophobic binding cavity than CyD itself and has different inclusion properties as a host molecule^{16,17} resulting in specific catalytic properties for C–C bond formations,^{18,19} the use of the immobilized CyD as selective catalysts for the present and the analogous reactions are under investigation.

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- The association constants of α - and β -CyD are 19^{12} and 101^{13} mol⁻¹ dm³, respectively. This tendency was reported with other kinds of guest molecules.⁵
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